SECTION 3
FDA SUMMARIES

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1.0 Lead Reviewer & Engineering Summary

Date: July 24, 2001

From: Donna Buckley, Mechanical Engineer
CDRH/ODE/DCRD/ICDB

Subject: CardioSEAL® Septal Occlusion System with Qwik Load – VSD Indication

1.1 PMA Chronology

November 16, 2000	P000049 received by CDRH/ODE
January 8, 2001	P000049 filed
March 15, 2001	Letter sent to sponsor from FDA requesting additional information
June 15, 2001	Response to FDA's March 15th letter received
September 10, 2001	P000049 Scheduled for Review by Circulatory Systems Devices Panel

1.2 Summary

This PMA has been submitted in order to seek marketing approval for the CardioSEAL® Septal Occlusion Device with Qwik Load for the treatment of complex ventricular septal defects (VSDs) of a significant size to warrant closure, but that based on location, cannot be closed with standard transatrial or transarterial approaches. The device is currently approved under a Humanitarian Device Exemptions (HDE) application (H990005; approved 9/28/99) for the same indication proposed in this PMA. (See attached guidance document for more information on HDE regulation. Also, see attached Summary of Safety and Probable Benefit for the CardioSEAL® device.)

The pivotal cohort of patients used to support PMA approval was generated from patients enrolled in the "Multicenter Trial to Study the Bard Clamshell II/ CardioSEAL® Septal Occluder in High Risk Patients," sponsored by Boston Children's Hospital (IDE G930120). The current report of this ongoing study includes patients with various anatomic defects enrolled between 5/14/96 and 2/1/00 at five participating institutions. All patients enrolled in this study were considered to be high-risk for surgical closure, due to either complex medical or cardiac disease. Devices used in the study were obtained from C.R. Bard (Clamshell I, Clamshell II) and from Nitinol Medical Technologies, Inc. (CardioSEAL®). NMT Medical is seeking approval to market only the CardioSEAL® device. The Clamshell devices are earlier models of the CardioSEAL® technology. After NMT Medical purchased the Clamshell II device, it was renamed "CardioSEAL." The permanent implant in the CardioSEAL® and Clamshell II devices is the same; however, improvements were made to the delivery system. The Clamshell I design is the first generation model and includes a different permanent implant and delivery system; however, several general design characteristics are the same (e.g., double umbrella design, metal supporting arms, with metal supporting arms).

A total of 74 enrolled patients comprise the pivotal cohort. Of these 74 patients, the CardioSEAL® device was placed in 57 patients. More than one device was placed in 26 of the 57 patients for a total of 107 implanted devices. All but one patient in the pivotal cohort were enrolled at a single center. In addition to the pivotal cohort, the sponsor has provided supporting data for other indications and earlier device models. Table 1 summarizes the patient cohorts.

Safety

In order to evaluate safety, adverse events were recorded and categorized as serious, moderately serious, not serious, and unknown seriousness. Events were also categorized as device related, implantation related, or catheterization related. The results from the pivotal trial showed that 74.1% (43/58) of patients followed to 6 months experienced a major complication (defined as serious or moderately serious). Device-related

adverse events occurred in 17.2% (10/58) of patients and procedure-related adverse events occurred in 58.6% (34/58) patients at 6 months. (See Table B.16 in Section 5.D.1 for a list of events.)

	PATIENT SELECTION CRITERIA	DEVICE USED	PATIENT ENROLLMENT
PIVOTAL COHORT	congenital or post-operative residual VSD	CardioSEAL	enrolled: N=74 implant attempted: N=61 device placed: N= 57
SUPPORTING COHORTS	VSD acquired following myocardial infarction	CardioSEAL, Clamshell II	enrolled: N=7 implant attempted: 6 device placed: 5
	VSD (congenital, post-operative, acquired following myocardial infarction)	Clamshell I	enrolled/implant attempted* device placed: N=87
	atrial septal defect (ASD), patent foramen ovale (PFO), Fenestrated Fontan (FF), other defects	CardioSEAL, ClamShell II	enrolled: N=357 implant attempted: N=309 device placed: N=271
	atrial septal defect (ASD), patent foramen ovale (PFO), Fenestrated Fontan (FF), other defects	Clamshell I	enrolled/implant attempted* device placed: N=414

* Data were not recorded or are unreliable. Data were collected retrospectively for this follow-up study.

Table 1: Summary of Patient Cohorts

Efficacy

A "Clinical Status Scale" (page 9, Section 5.C) was used to evaluate efficacy. The primary efficacy evaluation includes a comparison of pre-procedure and 6-month defect closure using both the L to R shunt and anatomic categories from the Clinical Status Scale ("Clinical Status by Lesion Measure"). See Table 2 below. At 6 months, 84.1% of patients had at least a one point increase in clinical status, 2.3% of patients had no change in clinical status and 13.6% had at least a one point decrease in clinical status using the Clinical Status by Lesion Measure. (Note that explants and patient deaths are included in those patients that had a decrease in clinical status.) Overall, a median improvement of approximately 2 categories was noted for patients assessed at 6 months.

	Category	0	1	2	3	4	5
2	**L→R shunt**	Ventilator dependent and/or intractable CHF	Heart failure with symptoms	Left ventricular volume overload, large shunt	Moderate shunt	Small shunt	Trivial or no shunt
3	**Anatomic**	Ventilator dependent and/or intractable CHF	VSD diameter > 70% of aortic root diameter	VSD diameter 50-70% of aortic root diameter	VSD diameter 30-50% of aortic root diameter	VSD diameter 10-30% of aortic root diameter	VSD diameter < 10% of aortic root diameter

Table 2: Clinical Status by Lesion

These data provide the basis for the analyses presented in this panel pack. The clinical investigation information is summarized in the Clinical Summary and Statistical Summary provided by John E. Stuhlmuller, M.D. and R. Lakshmi Vishnuvajjala, Ph.D., respectively.

1.3 Device Description

The CardioSEAL® Septal Occlusion System with Qwik Load consists of a permanent implant component and a delivery catheter.

The CardioSEAL® device is constructed of a metal (MP35N) framework to which polyester fabric is attached. The framework is in a "double-umbrella" configuration where the two "umbrellas" sandwich the cardiac defect. Each umbrella consists of knitted polyester fabric supported by and fastened to four wire spring arms by polyester sutures. Radiopaque markers on the spring arms allow for better fluoroscopic visualization and a pin attachment is included in the center of the device for attachment to and release from the delivery system. The implant is packaged attached to a loading device, called the Qwik Load. The Qwik Load collapses the implant in order to facilitate placement inside the delivery sheath. The implant

is manufactured in 4 sizes: 17 mm, 23 mm, 28 mm, and 33 mm. The sponsor recommends that device sizes should be selected such that the CardioSEAL® to stretched diameter defect ratio is 1.7-2.0 to 1.0.

The delivery catheter is a 10F coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the occluder to the defect.

The evolution of the CardioSEAL® product is summarized in Table 3. Note again that the sponsor is only seeking approval to market the CardioSeal-QL device model.

 Evolution of Product	**Clamshell I**	• obsolete design that was manufactured by Bard • arms made of 304V stainless steel • one joint coil per arm • wire diameter = 0.010”
	Clamshell II	• arm material changed to MP35N • arm configuration modified to include both an “elbow” and “wrist” coil per arm, and • wire diameter = 0.009”
	CardioSEAL	• same as Clamshell II
	CardioSEAL-SF	• SF = “StarFlex” implant model • added a nitinol centering spring to the design of the implant
	CardioSEAL-QL	• loading device was modified to QL = “Qwik Load” system • no changes were made to the implants
	CardioSEAL-SF-QL	• StarFlex model with Qwik Load

Table 3: Evolution of Product

1.4 Bench Testing

The bench tests conducted using finished, sterilized devices, are summarized in Table 4. Bench testing was previously reviewed in the HDE application and is believed to support the adequacy of basic performance characteristics.

IMPLANT	DELIVERY SYSTEM	DELIVERY SYSTEM AND IMPLANT
• Spring Arm Fatigue* • Finite Element Analysis* • Arm/Fabric Strength Testing • Dislodgement Resistance Testing • Arm/Body Joint Strength Testing • Ball/Body Joint Strength Testing • Qwik Loader Funnel to Shaft Tensile Testing • MRI Compatibility Testing • Chemical Analysis of Implant Materials • MP35N Wire Mechanical Properties-Tensile and Elongation Testing • MP35N Wire Mechanical Properties-Corrosion Resistance Testing	• Control Clamp/Proximal Sleeve Joint Strength Testing • Control Clamp/Handle Sleeve Joint Strength Testing • Extrusion Luer/Shaft Tensile Testing • Extrusion Sub-Assembly/Marker Band Tensile Testing • Handle Sleeve/Core Wire Tensile Testing • Locking Collar/Y-body Torsion Testing	• Ball-to-Ball Strength Testing • QL Locking Cap to QL Funnel Pod Leak Testing • Pivotability Testing • Simulated Use Load and Deployment Testing • Shelf Life Testing (4 year shelf life for implant; 2 year shelf life for delivery catheter)

* The fatigue resistance of the device was not demonstrated by test or analysis. Numerous spring arm fractures have been noted clinically.

Table 4: Bench Testing

The testing conducted indicates that the device samples tested performed within specification. Fatigue testing on the bench could not preclude the potential for spring arm fracture because the *in vitro* loading conditions applied may not have been representative of the range of actual *in vivo* load.

1.5 Biocompatibility Testing

Biocompatibility tests in accordance with ISO-10993, "Biological Evaluation of Medical Devices", were conducted on the Implant and the Delivery Catheters. Test results indicate that the device system is biocompatible. A summary of the tests conducted is included in Table 5.

TESTS CONDUCTED	DELIVERY SYSTEM	IMPLANT
cytotoxicity	✓	✓
sensitization	✓	✓
systemic toxicity	✓	✓
intracutaneous reactivity	✓	✓
pyrogenicity, material mediated	✓	✓
hemolysis	✓	✓
hemocompatibility	✓	✓
thromboresistance	✓	✓
mutagenicity		✓
muscle implantation	✓	✓
USP Physiochemical studies	✓	✓

Table 5: Summary of Biocompatibility Testing

1.6 Animal Testing

The animal testing conducted using finished, sterilized devices was previously reviewed in the HDE application. A summary of the testing is included in Table 6. No major safety issues were identified from the animal testing.

PRODUCT	TEST	TEST ARTICLE	SAMPLE SIZE	ANIMAL MODEL	RESULTS
Clamshell II	Chronic Animal Study (Phase 1)	Clamshell II Implant + Delivery System	9	Canine, ASD created via blade septostomy, + balloon dilation immediately prior to implant, explants at 1(n=6) & 6 months (n=3)	1 elbow fracture at 1 mo. Oversized devices placed in freshly created defects resulted in thrombosis.
	Chronic Animal Study (Phase 2)	Clamshell II Implant + Delivery System	5	Sheep, ASD created via transseptal puncture + balloon dilation 2 wks prior to implant, explants at 1 (n=3) & 3 months (n=2)	Acceptable histological response. No arm fractures. Friction lesions noted near suture coil. Thrombus on 2/5 @ 1 month & 1/5 @ 3 months[1].
	Chronic Animal Study (Phase 3)	Clamshell II Implant + Delivery System	20	Canine, ASD created via blade septostomy, + balloon dilation 2wk prior to implant, explants at 2wks (n=4), 1mo (n=6), 3 mo (n=3), 6 mo (n=3), 12 mo (n=4), 24 mo (n=2)	Acceptable histological response. 1 elbow coil fracture @ 1 month. Tissue ingrowth & endothelialization complete by 3 months. Well tolerated in canine heart, eliciting normal healing response.
CardioSEAL -FLDS[2] Delivery System	Acute Animal Study	CardioSEAL – FLDS Delivery System	12	Sheep, acute, ASD created via transseptal puncture + balloon dilation	Delivery System met performance requirements.

1. Heparin was administered during the procedure. No anticoagulants were administered post placement.
2. Additional testing was not conducted on the Qwik Load component; however, adequate bench testing was provided.

Table 6: Animal Testing

1.7 Sterility Testing and Package Integrity

The CardioSEAL® Septal Occlusion System with Qwik Load is sterilized using a 100% ETO cycle that has been validated to achieve an SAL of 10^{-6} in accordance with ANSI/AAMI/ISO 11135-1994. Sterilization residual limits meet the requirements of ANSI/AAMI/ISO 10993-9:1995. Shipping and package tests were also conducted and all units met test acceptance criteria.

1.8 Device Failures and Malfunctions - Clinical Use

Device arm fractures were noted post implantation in 15.9% (17/107) of the devices implanted in the pivotal study; however, no adverse events were attributed to the occurrence of a device arm fracture. Although, conceptually, ulceration, perforation, patch migration, and embolization, are possible consequences of fracture, these events were not noted in the pivotal data set as a result of arm fracture. (Note that there were multiple device embolizations and percutaneous retrievals in one patient unrelated to fracture. No other embolizations were reported.) With the exception of a couple short term ulcerations that appear to have been related to fractures of an earlier device model (ClamShell I), fractures do not appear to be correlated with the occurrence of adverse events for this device design.

Device implant was attempted in 58 patients and a total of 107 devices were implanted with 6 patients receiving multiple devices. During these procedures, an additional 20 devices were either discarded or returned to the company after being loaded and/or inserted. Kinks in the delivery sheath, incorrect positioning, and inability to pass the delivery system were the primary reasons for not implanting the devices.

1.9 Conclusions

- The preclinical information was previously reviewed in the HDE application. No data have been presented that indicate a clear safety concern in the clinical setting regarding mechanical device failure or malfunction.
- There have been several incidents of device fracture; however, these events do not appear to be correlated with adverse clinical outcomes. Long term outcome for the device is unknown.

2.0 Clinical Summary

Date: July 2, 2001

From: John E. Stuhlmuller, M.D.
CDRH/ODE/DCRD/ICDB

Subject: NMT Medical CardioSEAL® Septal Occlusion System with Qwik Load
Indication for Use-Closure of Ventricular Septal Defects

2.1 Introduction

Clinical data contained in this PMA was collected between May 1996 and February 2000 under a sponsor-investigator IDE (Boston Children's Hospital, number G930210) in an open-label, single-arm, registry entitled "Multicenter Trial to Study the Bard Clamshell II/CardioSEAL Septal Occluder in High-Risk Patients".

This registry was initiated prior to the Expanded Access provisions of the Food and Drug Administration Modernization Act of 1997. The High-Risk registry investigational plan meets the criteria for individual patient access to investigational devices intended for serious diseases also referred to as compassionate use. The criteria for compassionate use include the following:

1. A description of the patients condition and the circumstances necessitating treatment;
2. A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed.

In the case of the High-Risk registry, a description of the patients condition and circumstances necessitating treatment was provided by a study investigator for review by an independent interventional cardiologist and cardiac surgeon. The independent physician review evaluated the probable risk of using the investigational device versus the probable risk from the disease or condition and whether alternative therapies were unsatisfactory. As noted in Section 5, in the event that patients were eligible for treatment in another investigational device study, patient were enrolled in that study. Consequently, patients enrolled in this registry were considered to have no other satisfactory alternative therapies. Appropriate patient protection measures were followed. Patient protection measures included IRB review of the investigational plan, patient informed consent, and patient outcome review by a Data Safety Monitoring Board (DSMB).

The patient selection criteria included the following:

- Patients with one or more cardiac defects with sufficient hemodynamic derangement to warrant intervention and one of the two following criteria:
  1. A type of defect that is technically difficult or impossible to close surgically, such that the surgical risk are sufficient to justify the known and potential unknown risk of the device, or
  2. An overall medical condition such that the surgical risk are sufficient to justify the known and potential unknown risks of the device.
- Patient exclusion criteria related primarily to device related issues such as ability to achieve vascular access, device sizing, and relationship to device to other cardiac structure such as pulmonary veins and heart valves.

2.2 Ventricular Septal Defect-Pivotal Cohort (Section 5.D.1)

2.2.1 Registry Design

The pivotal data set represents a patient subset enrolled for closure of a congenital ventricular septal defect (VSD) in the High-Risk registry. The VSD could be previously unoperated or with post-operative residual shunting.

Patient selection criteria are discussed above.

2.2.2 Patient Outcome Assessment

Patient outcome assessment for effectiveness was completed using the Clinical Status Scale (CSS) developed by the investigators at Boston Children's Hospital. The CSS evaluated eight nominal variables each using an ordinal scale (0 to 6). The eight nominal variables included: right to left shunt, left to right shunt, anatomical size, presence of systemic embolization, hemodynamic compromise not due to shunt, arrythmias, pulmonary vascular resistance, and medical condition. The ordinal scale for each nominal variable was constructed so that a change in value of 1 constituted a clinically meaningful change.

	Category	0	1	2	3	4	5
1	**R→L shunt**	O_2 < 75% and/or ventilator dependent	O_2 < 80%	O_2 < 85%	$O_2 \leq 90\%$	O_2 > 90%	O_2 >95%
2	**L→R shunt**	Ventilator dependent and/or intractable CHF	Heart failure with symptoms	Left ventricular volume overload, large shunt	Moderate shunt	Small shunt	Trivial or no shunt
3	**Anatomic**	Ventilator dependent and/or intractable CHF	VSD diameter > 70% of aortic root diameter	VSD diameter 50-70% of aortic root diameter	VSD diameter 30-50% of aortic root diameter	VSD diameter 10-30% of aortic root diameter	VSD diameter < 10% of aortic root diameter
4	**Systemic embolism**		Recurrent embolic events on coumadin	Recurrent embolic events, No anticoagulation	Single embolic event	Potential for embolic event	No intracardiac potential for embolic event
5	**Hemodynamic compromise not due to shunt**	Ionotropic dependant	Severe CHF	Moderate CHF	Mild CHF	Minimal CHF	No CHF
6	**Arrhythmia**		Life-threatening	Difficult to control	Requiring medication	No medication	
7	**Elevated PVR**		PAP with PVR > 5.0	PAP with PVR > 2.0	PAP at risk for PVOD		
8	**Medical Illness**		Severe	Moderate/Severe	Moderate	Mild	

Patient follow-up was completed at 1-, 6-, 12-, and 24 months after device placement. Follow-up consisted of various combinations of clinical evaluation , fluoroscopy, echocardiography, and electrocardiography.

Adverse events were broadly categorized as related to the device, implantation procedure, catheterization or unrelated to device, implantation or catheterization. They were further characterized based on their severity (serious and non-serious) and time of occurrence after device placement. The study investigators completed initial classification. The DSMB subsequently adjudicated these events and determined whether the frequency of specific events represented a safety issue.

The sponsor has proposed evaluating safety and effectiveness based on patient follow-up at 6 months. The database was closed on 2/1/00 for information contained in this PMA.

2.2.3 Results

A total of 74 patients were enrolled for VSD closure. Device placement was attempted in 58 of 74 patients. Successful placement occurred in 57 of 58 patients. Unoperated defects were seen in 46% of patients and post-operative defects in 54%.

Patient demographic information reveals that 42% were male and almost 80% were less than 10 years of age. Significant pre-procedure arrhythmias were noted in 18%, elevated pulmonary vascular resistance in 35%, significant non-cardiac medical illness in 25%, coexisting cardiac condition in 60%.

Multiple procedures were performed in 6 patients and multiple devices implanted in 26 patients. Two device sizes accounted for 83% of devices implanted (17 mm and 23 mm).

All but one patient was enrolled at a single medical center.

Outcome assessment for effectiveness at the 6-month patient follow-up utilized the Clinical Status Scale outlined above. Pre-procedure and 6-month follow-up evaluation using the CSS was available for 44 of the 57 implanted patients. The Anatomical scale was used in 14 patients at both evaluations. The L to R shunt scale was used in 22 patients at both evaluations. The Anatomy scale was used pre-procedure and the L to R shunt scale was used at the 6-month follow-up in 8 patients. Other patients characteristics such as arrhythmias, elevated pulmonary vascular resistance and the overall medical condition of the patient were identified as significant factors contributing to device placement and are incorporated into the CSS. However, the sponsor has chosen to evaluate effectiveness using the Anatomical, L to Right Shunt or a combination of these two variables. Subgroup analysis based on etiology (previously unoperated versus post-operative) is provided.

Adverse events occurred in 57 of the 58 patients in whom device placement was attempted. Four patients died prior to 6-month follow-up. One of the four patients deaths was considered catheterization related. Two patient deaths were classified as related to the patients underlying cardiac disease. One patient death is classified as related to the patients underlying medical condition.

A total of 222 adverse events were reported with 32 device related, 35 implantation related, and 85 catheterization related. Moderately serious or serious events occurred in 22 patients (38%).

Device arm fractures are reported in 34 of 107 devices reported. No adverse events are categorized as fracture related. A separate analysis of device arm fractures is provided in Section 5.D.6.

Section 5.D.1 contains the sponsor's complete report for this patient cohort.

2.3 Non-Pivotal Patient Cohorts

Information for the following patient groups has been provided as non-pivotal data:

- Clamshell I Follow-up Study - Ventricular Septal Defect (Section 5.D.2)
- High-Risk Registry – Non-VSD patients (Section 5.D.3)
- Clamshell I Follow-up Study – Non-VSD patients (Section 5.D.4)
- Acquired VSD Following Myocardial Infarction (Section 5.D.5)

2.3.1 Clamshell I Follow-up Study - Ventricular Septal Defect (Section 5.D.2)

The Clamshell I Follow-up Study database was created in 1996 for patients who had a Clamshell I device implanted at Children's Hospital under a previous IDE study conducted by C.R. Bard or on an emergency use basis. This database contains information derived from retrospective review of patient records prior to 1996 and prospective information on late device performance obtained at the time clinical follow-up care since that time. The database is limited to patients in which a device has been implanted.

Device placement was successful in 87 of 93 patients. The types of VSD included unoperated (53%), post-operative residual shunting (32%) and acquired following myocardial infarction (15%).

Patient demographic information reveals that 46% were male. The mean age is 16 years of age with a range from 0.5 to 80 years. Patient follow-up extends to 11.5 years in some patients.

Multiple devices were implanted in 33 patients with a total of 140 devices implanted. All device sizes were implanted with the 17 mm and 23 mm accounting for 57% of devices implanted.

Adverse events are characterized as noted in Section 5.C. This classification is similar to that used in the High-Risk registry with adverse events being broadly characterized as related to the device, implantation procedure, catheterization or unrelated to device, implantation or catheterization. In addition, they were further characterized based on their severity (serious and non-serious), time of occurrence after device placement. Event adjudication was completed by the High-Risk registry principal investigator.

Adverse events occurred in 85 of the 93 patients in whom device placement was attempted. Seventeen patients have died during the follow-up period. All patient deaths are considered unrelated to the device or implantation procedure.

A total of 315 adverse events were reported over 386 person-years of follow-up with 25 device related, 7 implantation related, and 125 catheterization related. Moderately serious or serious events occurred in 21 patients (23%).

Device arm fractures are reported in 29 of 140 devices. Two adverse events are categorized as fracture related. A separate analysis of device arm fractures is provided in Section 5.D.6.

Section 5.D.2 contains the sponsor's complete report for this patient cohort.

2.3.2 High-Risk Registry – Non-VSD patients (Section 5.D.3)

A total of 357 patients were enrolled in the High-Risk registry for non-VSD cardiac defects. Indications for use included Fontan baffle fenestration (38%), patent foramen ovale (26%), atrial septal defect (24%) and other lesions (11%).

Patient selection, criteria for device placement, and outcome assessment are the similar to those outlined above for the VSD pivotal patient cohort.

Clinical evaluation and outcome assessment was completed using the CSS outlined above. Adverse events were evaluated and categorized in the manner discussed above for the VSD patient cohort.

Patient demographic information reveals that 51% were male. The mean age was 26 years with a range from 0.7 to 83 years of age.

Device placement was successful in 271of 274 patients. Multiple procedures were performed in 5 patients and multiple devices were implanted in 19 patients. All device sizes were implanted with the 17 mm and 23 mm accounting for 63% of devices implanted.

Outcome assessment for effectiveness at the 6-month patient follow-up utilized the Clinical Status Scale. Pre-procedure and 6-month follow-up evaluation using the CSS was available for 242 of the 271 implanted patients.

Adverse events occurred in 224 of the 274 patients in whom device placement was attempted. Twenty one patients died. Ten patient deaths were classified as related to the patients underlying cardiac disease. Eleven patient deaths were classified as related to the patients underlying medical condition. Six devices were explanted. Three were explanted after device embolization. Two device malpositions required explantation. Hemolysis lead to the other device removal.

A total of 639 events including device arm fractures were reported with 72 device related, 25 implantation related, and 157 catheterization related. Moderately serious or serious events occurred in 33 patients (12%).

Device arm fractures are reported in 34 of 297 devices. One adverse event was categorized as possibly fracture related. A separate analysis of device arm fractures is provided in Section 5.D.6.

Section 5.D.3 contains the sponsor's complete report for this patient cohort.

2.3.3 Clamshell I Follow-up Study – Non-VSD patients (Section 5.D.4)

This patient cohort is derived from the non-VSD patient cohort in the Clamshell I Follow-up Study described above.

Device implantation to close a lesion other than VSD was successful in 414 patients. Cardiac defects included atrial septal defects (ASD-44%), Fontan baffle fenestration (26%), patient foramen ovale (12%) and other lesions (18%). Atrial level defects were categorized as simple ASD; complex ASD with medical disease; complex ASD with cardiac disease; complex ASD with postoperative defect; and complex ASD after Fontan.

Follow-up has ranged from 0 to 11.3 years.

Patient demographic information reveals that 48% were male. The mean age was 18 years with a range from 0.3 to 85 years of age.

Device placement was successful in 414 of 415 patients. Multiple procedures were performed in 5 patients and multiple devices were implanted in 19 patients. All device sizes were implanted with the 17 mm and 23 mm accounting for 63% of devices implanted.

Adverse events are characterized as noted in Section 5.C. This classification is similar to that used in the High-Risk registry with adverse events being broadly characterized as related to the device, implantation procedure, catheterization or unrelated to device, implantation or catheterization. In addition, they were further characterized based on their severity (serious and non-serious), time of occurrence after device placement. Event adjudication was completed by the High-Risk registry principal investigator.

Adverse events occurred in 302 of the 415 patients in whom device placement was attempted. Forty one patients died. Twenty eight are considered unrelated to the device or procedure. Five deaths are possibly related to the device. One death is considered procedure related. The cause of death is unknown in 7 patients.

A total of 876 adverse events were reported over 2385 person-years of follow-up with 89 device related, 7 implantation related, and 138 catheterization related. Moderately serious or serious events occurred in 52 patients (13%).

Device arm fractures are reported in 120 of 450 devices. One patient had late destabilization possibly related to device arm fracture. Three patients developed intracardiac masses associated with device arm fracture requiring surgical removal. One fractured arm embolized to the right ventricle without known adverse effects A separate analysis of device arm fractures is provided in Section 5.D.6.

Section 5.D.4 contains the sponsor's complete report for this patient cohort.

2.3.4 Acquired Following Myocardial Infarction

Devices were implanted in 7 patients with an acquired VSD after myocardial infarction.

See Section 5.D.5 for additional information.

2.4 Fracture Analysis

2.4.1 High-Risk Registry

Combining all patients in the "High-Risk" registry, 274 of 333 patients with 335 implanted devices had adequate imaging for evaluation of device arm fracture. The overall fracture rate in this report is 16%. Fracture rate is related to device size and type of lesion in which the device was implanted.

The incidence based on device size is the following: 17 mm (4%), 23 mm (14%), 28 mm (18%), 33 mm (43%) and 40 mm (55%).

The incidence based on type of lesion is the following: VSD (19%), ASD (15%) and patent foramen ovale (40%), fenestrated Fontan (3%) and other (7%).

Probability of freedom from fracture was 94% at 6 months. Time to fracture was shorter for larger devices.

2.4.2 Clamshell I Follow-up Study

Combining all patients in the Clamshell I Follow-up study, 367 of 501 patients with 398 implanted devices had adequate imaging for evaluation of device arm fracture. The overall fracture rate in this patient cohort is 37%. Fracture rate is related to device size and type of lesion in which the device was implanted.

The incidence based on device size is the following: 17 mm (9%), 23 mm (33%), 28 mm (46%), 33 mm (73%) and 40 mm (82%).

The incidence based on type of lesion is the following: VSD (38%), ASD (59%) and patent foramen ovale (48%), fenestrated Fontan (2%) and other (27%).

Probability of freedom from fracture was 91% at 6 months and decreased to 54% at 8 years. Time to fracture was shorter for larger devices.

2.4.3 Adverse Clinical Events

Adverse clinical events related to device fracture are uncommon. No adverse events were noted in the VSD Pivotal Patient Cohort.

In the Clamshell I Follow-up Study, one patient presented with cyanosis due to late device destabilization possibly related to an arm fracture. Three patients developed intracardiac masses related to arm fracture that were removed surgically. In one case a fractured arm embolized to the right ventricle without adverse effects.

See Section 5.D.6 for additional information.

2.5 Issues for Panel Consideration

- No control group identified.
- Validation of Clinical Status Scale
- Evaluation of effectiveness (clinical benefit) using selected nominal variables contained in the Clinical Status Scale
- Evaluation of safety (clinical benefit versus risk) based on type and frequency of adverse events.

3.0 Statistical Summary

Date: July 2, 2001

From: R. Lakshmi Vishnuvajjala, Mathematical Statistician
CDRH/OSB/Division of Biostatistics

Subject: CardioSEAL Septal Occlusion System with QwikLoad, VSD indication – Statistical Review

3.1 Introduction

The CardioSEAL Septal Occlusion System is indicated for use in patients with a complex ventricular septal defect (VSD) of a significant size to warrant closure, but based on location cannot be closed with standard transatrial or transarterial approaches. The device is offered in four sizes (17mm, 23mm, 28mm and 33mm). This device has been previously approved for the same indication under HDE H990005.

Data for this study are from an ongoing one-arm study sponsored by Children's Hospital, Boston. The study includes patients at four participating institutions. The pivotal data for this study includes all patients enrolled in the High-Risk Study to close either a congenital, or a postoperative residual ventricular septal defect. The two non-pivotal cohorts are patients enrolled in the High-Risk Study for closure of a post-myocardial infarction VSD, and those in the Clamshell I Follow-up Study for closure of any VSD. Patients enrolled in either study for indications other than VSD are presented as supporting cohorts. Analyses of device arm fractures include all individuals enrolled in either the High Risk Study, or the Clamshell Follow-up Study with adequate images to detect or exclude device arm fracture.

3.1.1 Pivotal Study

The primary safety outcome is all moderately serious or serious device, implantation or catheterization-related events.

The primary effectiveness outcome is change in clinical status scale at six months. The scale was constructed so that an improvement by one category would be considered clinically meaningful.

There were a total of 74 patients in the High Risk study, and of these 14 did not have a device implanted. Three others received a STARflex device. The other 57 received Clamshell II or CardioSEAL, and device placement was successful in all 57. Multiple implantation procedures were performed in 6 patients, and multiple devices implanted in 26. Of the 107 devices implanted, 71 were CardioSEAL and 36 were Clamshell II.

Four patients died during the follow-up period, one due to the catheterization procedure and the other three due to underlying cardiac or medical conditions.

Four devices were explanted, two at the time of a heart transplant, one at a Fontan surgery performed after a failed septation, and one at a catheterization during which an unsuccessful attempt was made to close a large residual defect.

The adverse events are presented in tables B.1 through B.15 of the Panel Package (and on pages 2831-2838 of the PMA). There were 115 moderately serious or serious events. Of these, 79 occurred within two days, and another 17 in the first month. The other 19 occurred over the next five months.

There were 20 fractures, 4 prior to discharge, 8 from discharge to 6 months, and 8 from 6 months to the most recent follow-up.

The effectiveness data are presented in tables C.1 through C.3 (and on pages 2846-2852 of the PMA). Among the 57 implanted patients, 50 could be assessed according to the Clinical Status Scale at both pre-implantation and at the 6-month follow-up time point. In this group, the median change in scale values was an increase of 2 categories, and 84% of the procedures were successful at 6 months (had an improvement of at least one category). Eight patients were in a lower clinical status category than prior to implantation, including the four patients who died and two who had their device explanted.

3.1.2 Ventricular Septal Defect - Non-Pivotal Cohorts

Acquired following Myocardial Infarction

There were six patients and device placement was attempted in five. Of these, four implantations were successful and three could be assessed at both pre-implantation and at six-month follow-up according to the Clinical Status Scale, with all three being successful.

Clamshell Follow-up Study

In this study, device implantation to close a ventricular septal defect was successful in 87 patients. Apparently, it was attempted in 93 patients (not clearly mentioned). Median length of follow-up was 4.1 years, and 18 patients died during follow-up period. Device arm fractures were detected in 29 of 140 devices.

High Risk Study

A total of 358 patients were enrolled in the High Risk Study to close a lesion other than a ventricular septal defect. Device implantation was attempted in 275 patients and was successful in 272. A total of 298 devices were implanted, 266 CardioSEAL and 32 Clamshell II. Seventeen patients died during follow-up period. Of the 272 implanted patients, 228 could be assessed according to the Clinical Status Scale both pre-implantation and at the 6-month follow-up, and the median scale value increased by two categories in this group.

Clamshell I follow-up Study

In this study, device implantation to close a lesion other than a ventricular septal defect was successful in 414 (out of ?) patients. Median length of follow-up was 5.6 years and 38 patients died during the follow-up time. Twenty-five devices were explanted from 24 patients. Device arm fractures were detected in 120 of 450 devices.

Fracture Analysis

Combining all patients from the High Risk Study, including the pivotal, non-pivotal and supporting cohorts, 274 of 333 patients had imaging of sufficient quality to accurately assess whether the device arms were intact or fractured. A total of 337 devices were implanted in these 274 patients and the overall fracture rate was 15%, with a monotonic increase in fracture rate according to device size: 17mm (5%), 23mm (12%), 28mm (16%), 33mm (39%) and 40mm (55%). Fracture rates also varied by the type of lesion in which the device was implanted: ventricular septal defect (18%), atrial septal defect (15%), patent foramen ovale (37%), fenestrated fontan (2%), and other (7%). This variability by lesion type was less apparent after stratifying by device size.

3.2 Reviewer's Comments

Improvement by one category was determined to be a clinically acceptable measure of effectiveness. In the pivotal study, and High risk non-pivotal study, the median improvement was 2 categories.

Some of the percentages presented must be considered carefully. For example, the 2 category median change in the pivotal study was determined based on 50 patients who could be assessed at both pre-implantation and six-month follow-up. But it started with 74 patients, of whom 60 could be implanted, 57 with the sponsor's devices, and only 50 of them could be assessed at both time points.

The safety endpoint is based on moderately serious and serious events, and the acceptability of these numbers should be decided on a clinical basis. They were not compared to anything else.

The overall fracture rate is 15%, but it is 55% for the 40mm device. Again, this needs to be considered in view of the alternatives available to these patients.

3.3 Reviewer's Conclusions

The study met the effectiveness criterion. For safety, the acceptability of the number of moderately serious and serious adverse events should be decided on a clinical basis, since no comparisons were made to another device and no acceptable levels were defined prior to the trial.